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Comments Before the National Toxicology Program
Board of Scientific Counselor's Report on Carcinogens Subcommittee
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Greenpeace appreciates this opportunity to offer comments before this Subcommittee of the National Toxicology Program Board of Scientific Counselors and applauds the Program's commitment to public input and review.

1.0 TCDD: Evidence of Human Carcinogenicity

We endorse strongly the decision by the National Toxicology Program (NTP) to consider new scientific evidence as it considers the classification of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a human carcinogen and its subsequent inclusion in the *Report on Carcinogens.*

The recent classification of TCDD as a Group 1 carcinogen (carcinogenic to humans) by the International Agency for Research on Cancer lends considerable support for similar action by NTP, as does the conclusion by the Institute of Medicine that exposure to dioxin-contaminated herbicides correlates with elevated incidence of certain specific cancers.[1,2]

During its deliberations on dioxin reassessment, the U.S. Environmental Protection Agency (USEPA) presented the following scientific conclusion within the Agency itself:[3]

"Dioxin does cause cancer in humans."

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[1] Institute of Medicine, "Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam," Washington, D.C.: National Academy Press, 1993.

[2] Institute of Medicine, "Veterans and Agent Orange Update 1996," Washington, D.C.: National Academy Press, 1996.

[3] U.S. Environmental Protection Agency. Office of Research and Development. 1992. EPA's Scientific Reassessment of Dioxin: A Status Briefing for the Administrator, January 27, 1992. Washington, D.C.

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In its review of USEPA's draft dioxin reassessment, the USEPA Science Advisory Board noted:[4]

> *"Almost all Members of the Committee therefore concur with the judgment that 2,3,7,8-TCDD, under some conditions of exposure, is likely to increase human cancer incidence."*

As the Subcommittee is well aware, there is a compelling body of scientific research indicating that chlorinated dioxins, especially TCDD, and related chemicals such as the dibenzofurans, cause cancers in humans. For example, elevated overall cancer incidence has been reported in a number of studies involving large cohorts of chemical workers and pesticide applicators .[5,6,7,8] More recent studies have found positive correlations between cancer incidence and exposure to TCDD and other TCDD-like substances to be dose-dependent and to increase with latency period.[9,10,11]

In another recent study of more than 20,000 workers in 12 countries, exposure to TCDD-contaminated phenoxy herbicides was associated with increased mortality from soft-tissue sarcoma at twice the expected rate. Mortality from all malignant neoplasms, non-Hodgkin's lymphoma, and lung cancer was also found to increase with time since first exposure.[12]

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[4] U.S. Environmental Protection Agency Science Advisory Board. 1995. Science Advisory Board Review of EPA's Dioxin Reassessment. Executive Committee Review Draft. Washington, D.C., September 19, 1995..

[5] Fingerhut, M.A., Halperin, W.E., Marlow, D.A., Piacitelli, L.A., Honchar, P.A , Sweeney, M.H., Griefe, A.L.., Dill, P.A., Steenland, K., Suruda, A.J. 1991. Cancer Mortality in Workers Exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. N Eng J Med, 324: 212-218.

[6] Kogevinas, M., Saracci, R., Winkelmann, R., et al. 1993. Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Cancer Causes and Control 4: 547-553.

[7] Manz, A., J. Berger, J.H.Dwyer, D. Flesch-Janys, S. Nagel, H., Waltsgott. 1991. Cancer Mortality Among Workers in Chemical Plant Contaminated with Dioxin. Lancet.338 (8773): 959-964.

[8] Zober A., Messerer P. and Huber P. 1990. Thirty-four year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. Int. Arch. Occ. Environ. Health. 62: 139-157.

[9] Flesch-Janys, D., Berger, J., Gum, P., Manz, A., Nagel, S., Waltsgott, H., Dwyer, J.H. 1995. Exposure to polychlorinated dioxins and furans and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. Am. J. Epidemiol. 142(11):1165-1175.

[10] Becher, H., Flesch-Janys, D., Kauppinen, T., Kogenvinas, M., Steinforf, K., Manz, A., Wahrendorf, J. 1996. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Canc. Causes Control 7: 312-321.

[11] Ott, M., Zober, A. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after 1953 reactor accident. Occup. Environ. Med. 53: 606-612.

[12] Kogevinas, M., Becher, H., Benn, T., Bertazzi, P., Boffetta, P., Bueno-de-Mesquita, H.B., Coggon, D., Colin, D., Flesch-Janys, D., Fingerhut, M., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Matthews, J., Neuberger, M., Pearce, N., Saracci, R. 1997. Cancer mortality in workers exposed to phenoxy herbicides: An expanded and updated international cohort study. Am. J. Epidemiol. 145 (12): 1061-1075.

Based on substantial, compelling scientific evidence, much of which has also been drawn upon by IARC, Institute of Medicine, and USEPA in developing their positions on the issue of TCDD and human cancer, NTP should proceed with classifying TCDD as a human carcinogen and including TCDD in the *Report on Carcinogens.*

2.0 TCDD: Non-Cancer Effects

We also urge NTP to continue and strengthen the Program's consideration of non-cancer effects associated with exposure to TCDD and other TCDD-like substances. Many studies have shown an association between dioxin exposure and certain non-cancer effects in exposed adults as well as among the offspring of such adults.

As evidenced in the extensive review and analysis by DeVito et al. (1995), certain non-cancer effects of dioxin exposure of adults occur at or near so-called background levels.[13] TCDD exposure has been associated with systemic effects among adults such as cardiovascular and ischemic heart disease[14] and endocrine effects such as thyroid disease[15] and diabetes.[16] A positive correlation between TCDD exposure and increased risk of diabetes was reported by Sweeney et al. (1992).[17] In a recently published study of Air Force veterans exposed to TCDD in Agent Orange, glucose abnormalities and diabetes prevalence increased with exposure while time-to-diabetes-onset decreased.[18]

Immunological effects, including increased incidence of infectious disease, following adult exposure to TCDD, are also suggested in several studies.[19]

As reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR), reproductive effects associated with adult exposure to TCDD include

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[13] DeVito, M.J., Birnbaum, L.S., Farland, W.H., and Gasiewicz, T.A. 1995. Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. Environ. Health Persp. 103(3): 820-831.

[14] Flesch-Janys et al. (1995).

[15] Zober, A., Ott. M., Messerer, P. 1994. Morbidity follow up study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. Occup. Environ. Med. 51: 479-486.

[16] United States Air Force. 1991. Air Force health study: An epidemiological investigation of health effects in Air Force personnel following exposure to herbicides. Brooks Air Force Base, TX: U.S. Air Force.

[17] Sweeney, M.H., Hornung, R.W., Wall, D.K., et al. 1992. "Prevalence of diabetes and increased fasting serum glucose in workers with long-term exposure to 2,3,7,8-TCDD." Presented at 12th International Symposium on Dioxins and Related Compounds. August 3-28, 199, Tampere, Finland.

[18] Henriksen, G., Ketchum, N., Michalek, H., Swaby, J. 1997. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8(3): 252-258.

[19] U.S. Department of Health & Human Services, Agency for Toxic Substances and Disease Registry (ATSDR). 1997. "Toxicological Profile for Chlorinated Dibenzo-p-Dioxins." Draft. Atlanta, Georgia.

decreased testicular size, changes in hormone levels, increased spontaneous abortion, and alteration in sex ratio of children.[20]

A change in sex ratios such that more females than males were born occurred among certain segments of the population in Seveso, Italy,[21] and in Ufa, Russia.[22] Statistically significant excesses of female births have also been reported among populations near incinerators,[23] which are commonly recognized dioxin sources. Indeed, James (1997) has *"predicted that exposure to dioxin would be associated with the subsequent births of excess daughters."*[24] The relationship of dioxin and shifted sex ratios may be of particular importance given recent findings that the male proportion of live births in Canada and the U.S. have undergone a steady decline during the period 1970-1990, resulting in the "loss" of some 37,840 liveborn males.[25]

In interim policy guidelines on dioxin and dioxin-like compounds in soil, which were published this year, ATSDR points out: [26]

> *"[S]tudies have shown an association between development of subtle health effects ... in infants and their exposure to dioxin and dioxin-like chemicals from maternal milk ..."*

In an extensive analysis and review of effects of both prenatal exposure and postnatal exposure via breast milk, Brouwer et al. (1995) noted as follows: [27]

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[20] ATSDR (1997).

[21] Mocarelli, P., Brambilla, P., Gerthoux, P., Patterson, Jr., D., and Needham, L. 1996. Change in sex ratio with exposure to dioxin. Lancet 348: 409.

[22] Basharova, G. 1996. Reproduction in families of workers exposed to 2,4,5-T intoxication. Organohalogen Compounds 30:315-318.

[23] Williams F., Lawson A.; Lloyd O. 1991. Low sex-ratios of births In areas at risk from air-pollution from Incinerators, as shown by geographical analysis and 3-dimensional mapping. Int. J. Epidemiol. 21 (2): 311-319.

[24] James, W. 1997. Reproductive effects of male dioxin exposure: The use of offspring sex ratios to detect reproductive effects of male exposure to dioxins. Environ. Health Persp. 105 (2):162.

[25] Allan, B., Brant, R., Siedel, J., and Jarrell, J. 1997. Declining sex ratios in Canada. Can. Med. Assoc. J. 156 (1): 37-41.

[26] De Rosa, C., Brown, D., Dhara, R., Garrett, W., Hansen, H., Holler, J., Jones, D., Jordan-Izaguirre, D., O'Connor, R., Pohl, H., Xintaras, C. 1997. Dioxin and dioxin-like compounds in soil, Part II: Technical Support Document for ATSDR Interim Policy Guideline. J. Clean Technol., Environ. Toxicol., & Ocup. Med. 6 (2): 127-149.

[27] Brouwer, A., Ahlborg, U., Van den Berg, M., Birnbaum, L., Boersma, E., Bosveld, B., Denison, M., Gray, L., Hagmar, L., Holene, E., Huisman, M ., Jacobson, S., Jacobson, J., Koopman-Esseboom, C., Koppe, J., Kulig, B., Morse, D., Muckle, G., Peterson, R., Sauer, P., Seegal, R., Smits-Van Prooije, A., Touwen, B., Weisglas-Kuperus, N., and Winneke, G. 1995. Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. Eur. J. of Pharmacol. Environ. Toxicol. and Pharmacol. Sect. 293: 1-40.

"Relatively subtle adverse effects on neurobehavioral development and thyroid hormone alterations have also been observed in infants and children exposed to background levels. Exclusive use of the toxic equivalency factor (TEF) approach may underestimate the risk of neurodevelopmental effects, because both Ah receptor dependent and independent mechanisms may be involved in these effects. ...

Based on the present data set in experimental animals and the observation that human background body burdens are already in the range of the LOAELs for various functional developmental effects in animals, one may conclude that a certain proportion of the human population with background exposure to PCBs, PCDD/Fs mainly through dietary intake is already at risk for the occurrence of subtle functional developmental effects that are associated with these chemicals in laboratory animals."

Brouwer et al (1995) also observed that major endpoints of prenatal exposure included reduced birth weight, altered thyroid hormone levels, reduced psychomotor function, and deficits in cognitive function (infant and child). Pointing out that no threshold has been demonstrated for such effects, they also cautioned: [28]

"Effects on neurobehavioral development can be observed in human infants and children exposed to background levels of PCBs/PCDD/Fs in the diet. These effects are relatively subtle, and there is no evidence of gross malformation or retardation. Although these effects may not be detectable in the individual child, they may have implications at a populations level."

Recommendations

In summary, these and many other related studies reflect the need for NTP to proceed with a strong sense of urgency toward acquiring sufficient resources for a broad but thorough assessment of all health effects of TCDD and other TCDD-like chemicals. Such an assessment should serve as the basis for developing and implementing policies and regulations that have, as their objective, preventing the formation and release of TCDD and TCDD-like chemicals. In accordance with the high priority given by President Clinton and his Administration on the health and well-being of children, NTP should not only seek more resources but also allocate such resources so that the greatest emphasis is given to non-cancer effects, most urgently, the effects of exposure to TCDD and TCDD-like chemicals on the developing fetus and nursing infant as well as the young child and adolescent.

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[28] Brouwer et al. (1995).